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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/568,111

07/13/2006

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2101 7590 11/14/2008  
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EXAMINER

OLSON, ERIC

ART UNIT

PAPER NUMBER

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11/14/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/568,111	<b>Applicant(s)</b> HRECZUK-HIRST ET AL.	
	<b>Examiner</b> Eric S. Olson	<b>Art Unit</b> 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on 25 August 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 21-29 is/are pending in the application.
- 4a) Of the above claim(s) 11-19, 21, 22 and 25-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10, 23 and 24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

### **Detailed Action**

This office action is a response to applicant's communication submitted August 25, 2008 wherein claims 1-19, 21, and 22 are amended, claim 20 is cancelled, and new claims 23-29 are introduced. This application is a national stage application of PCT/GB04/03488, filed August 12, 2004, which claims priority to foreign applications EP03254988.3, filed August 12, 2003, and EP03255200.2, filed August 12, 2003.

### ***Election/Restrictions***

Applicant's provisional election with traverse of group I, claims 1-6, drawn to a polysaccharide having a pendant moiety, filed August 25, 2008, is acknowledged. Applicant's arguments of record with respect to the aforementioned traversal are acknowledged and found to be persuasive to remove the requirement for restriction between groups I and II, but not groups I-II and group III. Specifically, the subject matter of group II is merely a subspecies of the general teaching of claim 1 and does not lack unity of invention. However the additional limitation inserted by the amendment, that the pendant functional group contain two sialic acid residues attached by a 2.8 or 2.9 linkage, does not add any special technical feature not present in the prior art. As discussed below, this linkage is present in polysialic acid, a known naturally occurring polysaccharide that would be obvious to use in the methods of the prior art. Therefore this linkage does not constitute a shared special technical feature over the prior art.

Claims 11-19, 21, 22, and 25-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on July 25, 2008.

Claims 1-10 and 23, and 24 are pending in this application and examined on the merits herein.

### ***Specification***

The disclosure is objected to because of the following informalities: On p. 7, lines 27-30 of the specification, conjugates allegedly having a thioester group are discussed. This appears to be a typographical error in which the intended structure is a thioether group. While the specification makes numerous mentions of compounds conjugated to polypeptides by a thioether group there are no other references to thioester linkages. Furthermore, the aforementioned paragraph refers to a polysialic acid linked to a protein through an N-maleimide group which is converted to an N-succinimidyl group by reaction with a thiol. Reaction of a thiol with an N-maleimido compound form a thioether, not a thioester, as illustrated in figure 1 below. For these reasons it is believed that this occurrence of the term thioester is a typographical error.

Appropriate correction is required.

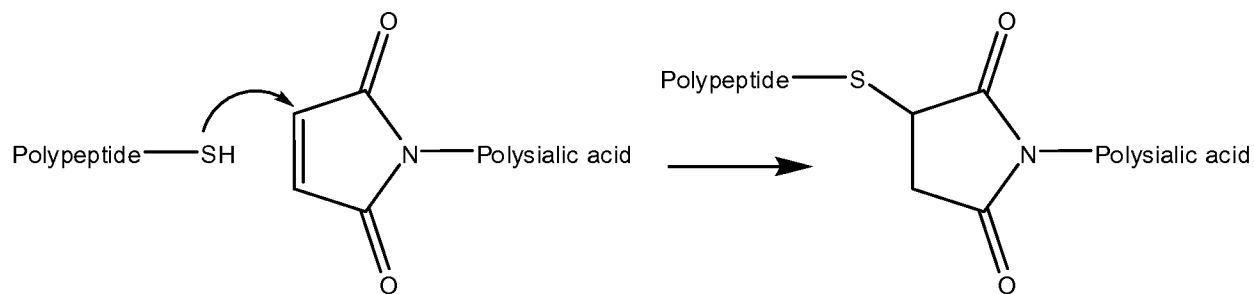


Figure 1 - Reaction of a thiol with a maleimido group forms a Succinimidyl thioether, not a thioester

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim is drawn to a polypeptide linked by a thioester bond to a polysialic acid. The specification as originally filed does not provide an written description of a conjugate linked by a thioester bond. Although p. 7 lines 27-30 of the specification contain the word "thioester" this appears to be a typographical error for reasons discussed above and this paragraph appears to be referring to thioether bonds. Nowhere are any actual reactions disclosed that would lead to a thioester linkage as opposed to a thioether. Therefore this claim lacks written description in the disclosure.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-8, 10, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Gregoriadis et al. (Reference included with PTO-892) in view of Ashkenazi et al. (5329028, of record in previous office action)

Gregoriadis et al. discloses polysialated asparaginase (p. 1967, left column second paragraph) This enzyme is conjugated to colominic acid, and is retained in physiological circulation longer than native enzyme while retaining most of its activity, making it a useful therapeutic protein. (p. 1968, right column) According to McGuire et al. (Reference included with PTO-892) colominic acid is a polysialic acid having 2,8 glycosidic linkages, a molecular weight of around 3000-4000 Da, and an average degree of polymerization of about 11. (See p. 249, right column paragraph 5 and p. 250 left column figure 1 of McGuire et al.) Because of the presence of a pendant triol chain at the nonreducing end of the polysialic acid, periodate oxidation will produce an aldehyde group at the nonreducing end which can be used for derivation. (p. 1966 of Gregoriadis et al., left column last paragraph) Figure 4 on p. 1966 of Gregoriadis et al. discloses a structure of the nonreducing end of polysialic acid showing that periodate oxidation introduces an aldehyde group at the 7- position. Coupling of a hydrazine moiety to this position would give a conjugate having the structure displayed in instant

claim 7. Therefore conjugates with colominic acid fit the requirements of the polysialic acid of the instant claims. Another polysialic acid (PSB) having 82 saccharide units is also disclosed to improve the biological half-life of fluorescein. (p. 1966, left column second paragraph) Gregoriadis et al. does not disclose compounds where the linker is an N-maleimide group attached to the nonreducing end of the polysialic acid which conjugates to a thiol group of the protein.

Ashkenazi et al. discloses bifunctional crosslinking reagents that can conjugate carbohydrates to thiol-containing proteins without compromising the activity of the protein. (column 5 lines 43-68) The crosslinking reagent comprises a hydrazine linked to a N-maleimide moiety by a hydrocarbon spacer of about 6-25 carbon atoms. Coupling is achieved by oxidizing the carbohydrate chain to aldehyde groups, reacting the aldehyde with the hydrazine moiety of the linker, and then reacting the carbohydrate-linker conjugate with the thiol group of the protein. (column 9 lines 7-18)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hydrazine-maleimide linker described by Ashkenazi et al. to conjugate the polysialic acids of Gregoriadis et al. (either colominic acid or low molecular weight PSB) with therapeutic proteins such as asparaginase. One of ordinary skill in the art would have been motivated to practice the invention in this manner in order to produce therapeutic proteins having improved *in vivo* persistence while maintaining good activity, in view of the fact that the inventions of Gregoriadis et al. and Ashkenazi et al. are directed toward modifying therapeutic proteins without hindering their activity. One of ordinary skill in the art would reasonably have expected success

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because both of the prior art references already demonstrate that these techniques lead to functional therapeutic proteins.

Therefore the invention taken as a whole is *prima facie* obvious.

### ***Conclusion***

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/  
Examiner, Art Unit 1623  
11/10/2008

/Shaojia Anna Jiang/  
Supervisory Patent Examiner, Art Unit 1623